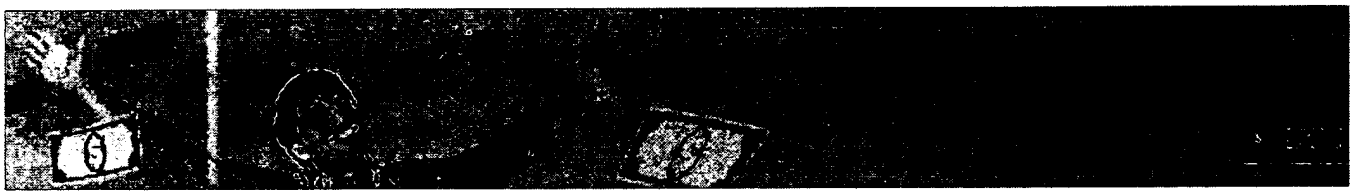

3 entries found for *nootropic.*

Main Entry: [1]**no·o·tro·pic**
Pronunciation: "nO-&-'trO-pik, -'träp-ik
Function: *adjective*
: of, relating to, or promoting the enhancement of cognition and memory and the facilitation of learning

Source: *Merriam-Webster's Medical Dictionary, © 2002 Merriam-Webster, Inc.*

Main Entry: [2]**nootropic**
Function: *noun*
: a nootropic substance and especially a drug <experimental use of *nootropics* to treat dementia> called also *smart drug*

Source: *Merriam-Webster's Medical Dictionary, © 2002 Merriam-Webster, Inc.*

Main Entry: nootropic
Part of Speech: *adjective, noun*
Definition: pertaining to a drug that enhances mental functions, such as memory
Etymology: Greek noos `mind' + -tropic `affecting'

1: Cereb Cortex. 2005 Jul;15(7):921-8. Epub 2004 Sep 30. Related Articles, Links

Full text article at cercor.oupjournals.org

Nootropic agents enhance the recruitment of fast GABAA inhibition in rat neocortex.

Ling DS, Benardo LS.

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It is widely believed that nootropic (cognition-enhancing) agents produce their therapeutic effects by augmenting excitatory synaptic transmission in cortical circuits, primarily through positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptors (AMPARs). However, GABA-mediated inhibition is also critical for cognition, and enhanced GABA function may be likewise therapeutic for cognitive disorders. Could nootropics act through such a mechanism as well? To address this question, we examined the effects of nootropic agents on excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs) recorded from layer V pyramidal cells in acute slices of somatosensory cortex. Aniracetam, a positive modulator of AMPA/kainate receptors, increased the peak amplitude of evoked EPSCs and the amplitude and duration of polysynaptic fast IPSCs, manifested as a greater total charge carried by IPSCs. As a result, the EPSC/IPSC ratio of total charge was decreased, representing a shift in the excitation-inhibition balance that favors inhibition. Aniracetam did not affect the magnitude of either monosynaptic IPSCs (mono-IPSCs) recorded in the presence of excitatory amino acid receptor antagonists, or miniature IPSCs (mIPSCs) recorded in the presence of tetrodotoxin. However, the duration of both mono-IPSCs and mIPSCs was prolonged, suggesting that aniracetam also directly modulates GABAergic transmission. Cyclothiazide, a preferential modulator of AMPAR function, enhanced the magnitude and duration of polysynaptic IPSCs, similar to aniracetam, but did not affect mono-IPSCs. Concanavalin A, a kainate receptor modulator, had little effect on EPSCs or IPSCs, suggesting there was no contribution from kainate receptor activity. These findings indicate that AMPAR modulators strengthen inhibition in neocortical pyramidal cells, most likely by altering

1: IDrugs. 2000 Sep;3(9):1053-63.

Potential clinical uses of neuroactive steroids.

Zorumski CF, Mennerick S, Isenberg KE, Covey DF.

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Neuroactive steroids rapidly modulate gamma-aminobutyric acid (GABA) and glutamate receptors. GABA-enhancing steroids have potential clinical utility as anesthetics, hypnotics, anticonvulsants and anxiolytics. Furthermore, GABAergic neurosteroids may participate in regulating mood and the effects of alcohol on the nervous system, suggesting a potential role in major psychiatric disorders. Neuroactive steroids that alter the function of glutamate receptors could be useful for treating neurodegenerative disorders, and as cognitive enhancers. Recent progress in developing water-soluble steroids and steroids with enhanced oral efficacy foster optimism that certain neuroactive steroids will be developed for clinical use.

PMID: 16049865 [PubMed]

1: Biochem Pharmacol. 2004 Oct 15;68(8):1479-87.

ELSEVIER FULL-TEXT ARTICLE

SGS742: the first GABA(B) receptor antagonist in clinical trials.

Froestl W, Gallagher M, Jenkins H, Madrid A, Melcher T, Teichman S, Mondadori CG, Pearlman R.

Neuroscience Research, Novartis Pharma AG, WKL-136.5.25, CH-4002 Basel, Switzerland. wolfgang.froestl@pharma.novartis.com

The GABA(B) receptor antagonist SGS742 (CGP36742) displays pronounced cognition enhancing effects in mice, young and old rats and in Rhesus monkeys in active and passive avoidance paradigms, in an eight-arm radial maze and a Morris water maze and in a social learning task. SGS742 blocks the late inhibitory postsynaptic potential and the paired-pulse inhibition of population spikes recorded from CA1 pyramidal neurons of the hippocampus of rats in vitro and in vivo. SGS742 significantly enhances the release of glutamate, aspartate, glycine and somatostatin in vivo. Chronic administration of SGS742 causes an up-regulation of GABA(B) receptors in the frontal cortex of rats. Single doses cause a significant enhancement of the mRNA and protein levels of NGF and BDNF in the cortex and hippocampus of rats. The observed antidepressant effects of SGS742 in rats may be explained by these findings. SGS742 was well tolerated in experimental animals as well as in young and elderly human volunteers with an absolute bioavailability in humans of 44%. In a Phase II double-blind, placebo-controlled study in 110 patients with mild cognitive impairment (MCI), oral administration of SGS742 at a dose of 600 mg t.i.d. for 8 weeks significantly improved attention, in particular choice reaction time and visual information processing as well as working memory measured as pattern recognition speed. A second Phase II clinical trial in 280 Alzheimer's disease patients is underway.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase I
- Clinical Trial, Phase II
- Randomized Controlled Trial

Your Search:

- Show **Drugs** with **Alzheimer's disease -- see under Dementia, Alzheimer's type** as an **Indication**

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Aricept ODT Tablets (Eisai)
Donepezil Hydrochloride
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Aricept Tablets (Eisai)
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Rivastigmine Tartrate
Exelon Oral Solution (Novartis)
Rivastigmine Tartrate
Namenda Tablets (Forest)
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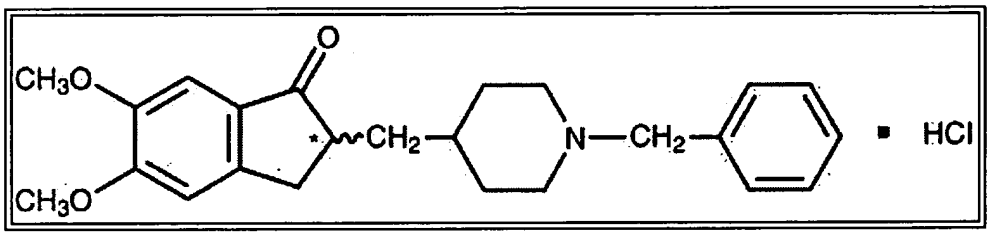
Razadyne ER Extended-Release Capsules (Janssen)
Galantamine Hydrobromide
Razadyne Oral Solution (Janssen)
Galantamine Hydrobromide
Razadyne Tablets (Janssen)
Galantamine Hydrobromide

PDR® entry for

ARICEPT® ODT (Eisai)
(donepezil hydrochloride)
Orally Disintegrating Tablets

DESCRIPTION

ARICEPT ® (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.



ARICEPT ® ODT tablets are available for oral administration. Each ARICEPT ® ODT tablet contains 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are carrageenan, mannitol, colloidal silicon dioxide and polyvinyl alcohol. Additionally, the 10 mg tablet contains ferric oxide (yellow) as a coloring agent.

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CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

Clinical Trial Data

The effectiveness of ARICEPT ® as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination >/= 10 and </= 26 and Clinical Dementia Rating of 1 or 2). The mean age of patients participating in ARICEPT ® trials was 73 years with a range of 50 to 94. Approximately 62% of patients were women and 38% were men. The racial distribution was white 95%, black 3% and other races 2%.

Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT ® was evaluated using a dual outcome assessment strategy.

The ability of ARICEPT ® to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher

Mechanism of Action

Pathological changes in Dementia of the Alzheimer type involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Exelon's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% five hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

Clinical Trial Data

The effectiveness of Exelon® (rivastigmine tartrate) as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) >/=10 and </=26, and the Global Deterioration Scale (GDS)]. The mean age of patients participating in Exelon trials was 73 years with a range of 41-95. Approximately 59% of patients were women and 41% were men. The racial distribution was Caucasian 87%, Black 4% and Other races 9%.

Study Outcome Measures: In each study, the effectiveness of Exelon was evaluated using a dual outcome assessment strategy.

The ability of Exelon to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 23 units, with a range from 1 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6-12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in Exelon trials was approximately 3-8 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the Exelon trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of three domains: patient cognition, behavior and functioning, including assessment of activities of daily living. It represents the assessment of a skilled clinician using validated scales based on his/her observation at interviews conducted separately with the patient and the caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

U.S. Twenty-Six-Week Study

Substrates of Microsomal Enzymes: *In vitro* studies indicated that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, CYP2C9, CYP2E1 and CYP3A4/5. In addition, *in vitro* studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Inhibitors of Microsomal Enzymes: Since memantine undergoes minimal metabolism, with the majority of the dose excreted unchanged in urine, an interaction between memantine and drugs that are inhibitors of CYP450 enzymes is unlikely. Coadministration of Namenda with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound.

Drugs Eliminated via Renal Mechanisms: Memantine is eliminated in part by tubular secretion. *In vivo* studies have shown that multiple doses of the diuretic hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the AUC of memantine at steady state. Memantine did not affect the bioavailability of TA, and decreased AUC and C_{max} of HCTZ by about 20%. Coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Memantine did not modify the serum glucose lowering effects of Glucovance®, indicating the absence of a pharmacodynamic interaction.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of memantine.

Drugs highly bound to plasma proteins: Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

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CLINICAL TRIALS

The effectiveness of Namenda (memantine hydrochloride) as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50-93 years. Approximately 66% of patients were female and 91% of patients were Caucasian.

A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint.

Study Outcome Measures: In each U.S. study, the effectiveness of Namenda was determined using both an instrument designed to evaluate overall function through caregiver-related assessment, and an instrument that measures cognition. Both studies showed that patients on Namenda experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator performs the inventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

The ability of Namenda to improve cognitive performance was assessed in both studies with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week St

Interview Based Impression of Change (CIBIC-plus).

The ability of RAZADYNE™ to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in RAZADYNE™ trials was approximately 4.5 units per year.

The ability of RAZADYNE™ to produce an overall clinical effect was